CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215814Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 9, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 215814
Product Name and Strength:	Rezlidhia (olutasidenib) Capsules, 150 mg
Applicant/Sponsor Name:	Forma Therapeutics, Inc. (Forma)
OSE RCM #:	2022-358-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Forma Therapeutics, Inc. (Forma) submitted a revised container label on November 9, 2022 for Rezlidhia (olutasidenib) capsules under NDA 215814. We reviewed the revised container label for Rezlidhia (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and in response to labeling recommendations from other review divisions.[a]

2 CONCLUSION

Forma Therapeutics, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Kane, D. Label and Labeling Review for Rezlidhia (NDA 215814). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 AUG 02. RCM No.: 2022-358.

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/s/

DEVIN R KANE
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HINA S MEHTA
11/14/2022 11:08:47 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 7, 2022
To:	Sheila Ryan, PharmD Regulatory Project Manager **Division of Hematologic Malignancies 1 (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Valerie Guerrier, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	REZLIDHIA (olutasidenib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 215814
Applicant:	Forma Therapeutics, Inc.

1 INTRODUCTION

On February 15, 2022, Forma Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215814 for REZLIDHIA (olutasidenib) capsules with proposed indication for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 1 (DHM1) on March 4, 2022 and February 22, 2022, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for REZLIDHIA (olutasidenib) capsules.

2 MATERIAL REVIEWED

- Draft REZLIDHIA (olutasidenib) capsules MG received on February 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 26, 2022.
- Draft REZLIDHIA (olutasidenib) capsules Prescribing Information (PI) received on February 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 26, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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VALERIE GUERRIER
11/07/2022 04:07:57 PM

LASHAWN M GRIFFITHS
11/08/2022 06:52:51 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 8, 2022

To: Sheila Ryan, Regulatory Project Manager,
Division of Hematologic Malignancies I (DHM1)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for REZLIDHIA™ (olutasidenib) capsules, for oral use

NDA: 215814

Background:

In response to DHM1's consult request dated February 22, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for REZLIDHIA™ (olutasidenib) capsules, for oral use.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 26, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on November 8, 2022.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on November 2, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (b) (6) or Valerie.Guerrier@fda.hhs.gov.

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/s/

VALERIE GUERRIER
11/08/2022 11:44:43 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 2, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 215814
Product Name, Dosage Form, and Strength:	Rezlidhia (olutasidenib) capsules, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Forma Therapeutics, Inc. (Forma)
FDA Received Date:	February 15, 2022 and May 6, 2022
OSE RCM #:	2022-358
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Forma Therapeutics, Inc. submitted NDA 215814 for Rezlidhia (olutasidenib) capsules on February 15, 2022. Rezlidhia is an isocitrate dehydrogenase-1 (IDH1) inhibitor proposed for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation. We evaluated the proposed Rezlidhia prescribing information (PI), container label, and Medication Guide for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Forma Therapeutics, Inc. submitted a 505(b)(1) application to obtain marketing approval of Rezlidhia (olutasidenib) capsules. We performed a risk assessment of the proposed prescribing information (PI), container label, and medication guide for Rezlidhia to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, Medication Guide and container label for Rezlidhia identified areas of vulnerability that may lead to medication errors. For the PI and Medication Guide, we recommend including statements in Section 2 Dosage and Administration and under "How Should I Take Rezlidhia" regarding not taking 2 doses within 8 hours, and not breaking, opening or chewing the capsules. For the container label, we recommend displaying the dosage form after the established name, revising the medication guide statement, and revising the proposed expiration date format. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Rezlidhia prescribing information, Medication Guide and container label identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Forma Therapeutics, Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. Section 2: Dosage and Administration

a. As currently presented, Section 2.2 Recommended Dosage states that Rezlidhia capsules should be swallowed whole. We recommend including the statement "Do not break, open or chew the capsules" after the swallow whole statement.

b. We note Section 2.2 Recommended Dosage states a missed dose of Rezlidhia should be taken "...as soon as possible and at least 8 hours prior to the next scheduled dose". We recommend including the statement "Do not administer 2 doses within 8 hours".

B. Medication Guide

1. We note under "How Should I take Rezlidhia" the Medication Guide states to "Swallow Rezlidhia capsules whole". We recommend including the statement "Do not break, open or chew the capsules" as part of this bullet point.

2. As currently presented, the sixth bullet under "How Should I take Rezlidhia" instructs the end user to take a missed dose "...as soon as possible and at least 8 hours before your next dose". We recommend including the statement "Do not take 2 doses of Rezlidhia within 8 hours" as part of this bullet point.

4.2 RECOMMENDATIONS FOR FORMA THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. We note the proposed Rezlidhia drug product will be available as capsules. As currently presented, the proposed finished dosage form is not presented on the proposed container label. In accordance with the *USP Nomenclature Guidelines*, we recommend including the dosage form on the principal display panel.

2. As currently presented, the proposed container label states (b) (4) and does not state how the medication guide will be provided. We recommend revising this statement to read "Dispense the enclosed Medication Guide to each patient" or a similar statement in accordance with 21 CFR 208.24(d).

3. We note the side panel of the proposed container label contains the statement (b) (4) We recommend revising this statement to read "Recommended Dosage: See Prescribing Information.".

4. As currently presented, (b) (4) We recommend (b) (4) (b) (4) presenting the statement as "Rx Only".

5. We note the proposed container label does not include a statement describing the contents of each Rezlidhia capsules. We recommend including the statement "Each capsule contains: 150 mg of olutasidenib" on the proposed container label.

6. As currently presented, the format for the expiration date is displayed on the proposed container label as "MMM-YYYY". FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

7. We note each of the Rezlidhia capsules are to be swallowed whole. We recommend including the statements "Swallow capsules whole. Do not break, open or chew capsules" on the container label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rezlidhia received on February 15, 2022 from Forma Therapeutics, Inc..

Table 2. Relevant Product Information for Rezlidhia	
Initial Approval Date	N/A
Active Ingredient	olutasidenib
Indication	REZLIDHIA is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation.
Route of Administration	Oral
Dosage Form	capsules
Strength	150 mg
Dose and Frequency	150 mg orally every 12 hours, until disease progression or unacceptable toxicity. Take on an empty stomach at least (b) (4) (b) (4) before or 2 hours after food.
How Supplied	(b) (4)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Rezlidhia labels and labeling submitted by Forma Therapeutics, Inc..

- Container label received on May 6, 2022
- Prescribing Information and Medication Guide (Image not shown) received on February 15, 2022, available from \\CDSESUB1\evsprod\nda215814\0001\m1\us\annotated.pdf

G.2Label and Labeling Images

- Container Label

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEVIN R KANE
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CLINICAL INSPECTION SUMMARY

Date	July 27, 2022
From	Anthony Orencia M.D., Ph.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ashley Woods, M.D., M.S., Medical Officer Kelly Norsworthy, M.D., Medical Team Leader R. Angelo de Claro, M.D., Division Director Sheila Ryan, Pharm.D., Regulatory Health Project Manager Division of Hematologic Malignancies 1 (DHM1) Office of Oncology Drugs (OOD)
NDA	NDA 215814
Applicant	Forma Therapeutics, Inc.
Drug	Olutasidenib (Rezildhia™)
NME	Yes
Division Classification	Isocitrate dehydrogenase 1 (IDH1) inhibitor
Proposed Indication	Treatment of adult patients with relapse/refractory acute myeloid leukemia with a susceptible IDH1 mutation
Review Type	Standard
Consultation Request Date	February 28, 2022
Summary Goal Date	August 1, 2022
PDUFA Date	February 15, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 2102-HEM-101 were submitted to the Agency in support of a New Drug Application for the drug olutasidenib, proposed for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with a susceptible isocitrate dehydrogenase isoform 1 (IDH1) mutation. Two clinical investigator sites (Karen Yee, M.D. and Stephane de Botton, M.D.) were inspected for Study 2102-HEM-101. Forma Therapeutics, Inc. was also inspected for its oversight and monitoring responsibilities as the study sponsor.

The study data derived from the above clinical investigator sites were considered reliable based on the inspections. Sponsor's monitoring and oversight of Study 2102-HEM-101 were adequate. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Olutasidenib is proposed for the treatment of relapsed/refractory acute myeloid leukemia, for patients with an IDH1 mutation. The disease complex is characterized by immature myeloid blasts in the bone marrow, that could interfere with normal hematopoiesis and accumulate in peripheral blood and other systems.

IDH1 mutations (IDH1m) in acute myeloid mutations are seen more often in older patients and patients with intermediate risk cytogenetics, higher platelet count, and increased bone marrow blast percent at diagnosis. The condition portends a worse prognosis in IDH1m acute myeloid leukemia patients, and poor overall survival in relapse/refractory acute myeloid leukemia.

A single clinical trial (Study 2102-HEM-101) was submitted in support of the applicant's NDA for accelerated approval. For this NDA under the PDUFA program review, CDER DHM1 requested clinical inspections at two large enrolling clinical investigator sites and sponsor site for the study.

Study 2102-HEM-101

Study 2102-HEM-101 was an open-label, multicenter study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of olutasidenib as a single agent or in combination with azacitidine or cytarabine in adult patients with acute myeloid leukemia or myelodysplastic syndrome. A Phase 1 dose-escalation stage, a Phase 1 dose-expansion stage, and a Phase 2 stage comprised the phased-in stages of this clinical investigative study. Olutasidenib 150 mg BID was determined to be the recommended Phase 2 dose (RP2D) for single-agent and combination treatment.

The primary objectives for this study were to evaluate the antileukemic and anti-myelodysplastic activity of olutasidenib as a single agent in patients with acute myeloid leukemia (AML) harboring an IDH1-R132 mutation.

The primary efficacy for olutasidenib was evaluated in the Phase 2 Cohort 1 of the study. The primary efficacy endpoint for Phase 2 Cohort 1 was complete remission plus complete remission with partial hematological recovery (best overall response [BOR] of CR/CRh) as determined by the investigator. The clinical activity of olutasidenib was evaluated using disease-specific criteria derived by the investigator from the IWG/modified IWG criteria for AML (Cheson, et al. 2003; Cheson, et al. 2006).

This study was conducted at 57 study centers, 47 of which enrolled Phase 2 Cohort 1 patients: 13 in the United States, four in Australia, one in Canada, ten in France, three in Germany, five in Italy, two in the Republic of Korea, five in Spain, and four in the United Kingdom.

The first patient enrolled on (b) (4) The first patient enrolled in Phase 2 Cohort 1 on (b) (4) (b) (4) The data cutoff date for safety and efficacy analyses was June 18, 2020. A total of 153 patients enrolled in the Phase 2 Cohort 1 and received at least one dose of olutasidenib as June 18, 2020. The study is ongoing.

Clinical inspections have focused on the Phase 2 Cohort 1 part of the study for verification of the efficacy and safety data submitted by the applicant for the proposed indication.

III. RESULTS (by site)

1. Karen Yee, M.D. /Study 2102-HEM-101/Site 100

Princess Margaret Cancer Centre
University Health Network
610 University Avenue, Suite 5-218
Toronto, Ontario M5G2M9
Canada

Inspection dates: May 2 to 6, 2022

For Phase 2 Cohort 1 of the study, eight subjects were screened, eight subjects were enrolled at the site. Of the enrolled subjects, all eight subjects completed the treatment phase of the study.

Study files assessed included a review of the Institutional Review Board (IRB) oversight and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, case report forms and test article accountability.

The site inspection also involved an evaluation of subject source records such as medical history, patient eligibility, laboratory results, blood sample records, ancillary procedures including bone marrow aspiration, adverse event and serious adverse event documentation and subject-specific protocol deviation records.

The primary efficacy endpoint data were verifiable. No under-reporting of serious adverse events was found. In general, no significant discrepancies were noted. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

The inspection found that a few non-serious adverse events were not reported to the FDA. For instance, Subject # (b) (6) had musculoskeletal shoulder and hand pain, myalgia, non-cardiac chest pain, and episodes of heart palpitation and anxiety with left upper arm pain during a cardiology clinic-related visit. Subject # (b) (6) had loss of appetite, vomiting and pain at an unspecified location.

Reviewer's comment: The unreported non-serious adverse events were likely related to AML itself rather than the investigative drug product. Therefore, the safety profile of the investigative drug product is less likely to be impacted.

2. Stephane de Botton, M.D./Study 2102-HEM-101/Site 331
Institut Gustave Roussy, Institut de Cancerologie
114 rue Edouard Vaillant
Villejuif Cedex, 94805, France

Inspection dates: June 27 to July 1, 2022

Of the total 26 study subjects that were screened in Study 2102-HEM-101 at this site, and 20 patients were enrolled in Phase 2 cohort 1 of the study. The study is ongoing, with four subjects currently receiving treatment. No subjects in the study withdrew consent. The enrolled subjects' records were evaluated for this study site audit.

Records reviewed involved the following items: independent ethics committee approvals, informed consent forms, financial disclosure forms, training records, screening and enrollment log, monitoring reports, subject source records, test article control records, and regulatory binder containing correspondences.

Patient source records were reviewed for all enrolled subjects in this study. Source documents were a combination of paper-based and electronic medical records. The reviewed source records included eligibility, medical history, lab requisitions, nursing notes, electrocardiograms, and bone marrow aspirate results, bone marrow procedure-based results, laboratory reports, non-serious adverse events, serious adverse events and efficacy data.

The efficacy data in the source records were verified against the data in the patient line listings submitted in the NDA. No discrepancies were found. No under-reporting of serious adverse events was found. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

The inspection found some transcription errors in the percentages of cell types such as myelocytes/metamyelocytes and segmented neutrophils/band forms in bone marrow aspirate laboratory reports, from the source data to the electronic CRFs.

Reviewer's comment: These transcription errors unlikely have a significant impact on the primary efficacy endpoint assessment of the study.

3. Forma Therapeutics, Inc. /Sponsor
300 North Beacon Street, Suite 501
Watertown, MA 02472

Inspection dates: April 4 to 7, 2022

The inspection assessed the application sponsor's oversight responsibilities for Study 2102-HEM-101.

The inspection included review of the trial master files, organizational charts, standard operating procedures, operational manuals, contracts, transfers of obligations, site monitoring, case report forms, handling of adverse events, data collection, and how the sponsor brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, monitoring procedures and frequency, other monitoring-related activities, test articles and test accountability records.

Monitoring of the study was conducted by (b) (4) the sponsor's CRO. The CRO was responsible for the clinical site evaluation visits, and oversight activities, in part, were reviewed during the inspection.

Monitoring was conducted in person at the study site and the electronic data capture system was monitored remotely. Prior to on-site visits, monitors sent notifications to the study site of their upcoming visit. After the visit, the monitor composed a monitoring visit letter. Protocol deviations were reviewed by (b) (4) and Forma, including meetings during which review of protocol deviations occurred. Forma made the final determination on the classification of all protocol deviations. Procedures for escalating any potential issues and handling of noncompliance were implemented.

The inspection found that sponsor provided adequate oversight and performed its responsibilities according to the FDA regulatory requirements. No evidence of under-reporting of adverse events was found. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

In general, the oversight and monitoring of Study 2102-HEM-101 appeared adequate.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Director, Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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MIN LU
07/27/2022 02:28:48 PM

JENN W SELLERS
07/27/2022 04:13:36 PM

Consult Memorandum

Date:	June 2, 2022
To:	Sheila Ryan, RPM CDER/OND/ORO/DROOD and Ashley Woods, MD, Clinical Reviewer by CDER/OND/OOD/DHM1
From:	Brittany Aguila, PhD, CDRH/OPEQ/OHT7/DMGP/MGB
Through:	Pamela Ebrahimi, Ph.D., Deputy Branch Chief, CDRH/OPEQ/OHT7/DMGP/MGB, Donna Roscoe, Ph.D., Deputy Director, CDRH/OPEQ/OHT7/DMGP, and Wendy Rubinstein, MD, Ph.D., Acting Director, CDRH/OPEQ/OHT7/DMGP
ICC Number:	ICC2200210
Subject:	NDA 215814
Drug Name:	REZLIDHIA (olutasidenib)
Drug Sponsor	Forma Therapeutics
Biomarker(s):	IDH1 mutations in acute myeloid leukemia (AML)
Device Name:	Abbott RealTime IDH1 assay
Device Sponsor:	Abbott
Related Submissions:	P170041/S006, P170041

I. BACKGROUND and PURPOSE

This consult request was received on February 23, 2022.
CDER is requesting CDRH consult to review the companion diagnostic (CDx) information submitted with the new NDA 215814 for its acceptability. In the reviewer's guide submitted under NDA 215814, Forma states that a letter of authorization was included allowing CDRH to access IND 127313 and NDA 215814 and allowing Abbott to cross reference in support of P170041.

The CDx in relation to NDA 215814 is the Abbott RealTime IDH1 Assay and this information was submitted under P170041/S006.

II. PROPOSED INDICATION

The current approved IU for the Abbott assay is as follows (P170041):

Abbott RealTime IDH1 is an in vitro polymerase chain reaction (PCR) assay for the qualitative detection of single nucleotide variants (SNVs) coding five IDH1 R132 mutations (R132C, R132H, R132G, R132S, and R132L) in DNA extracted from human blood (EDTA) or bone marrow (EDTA). Abbott RealTime IDH1 is for use with the Abbott m2000rt System. Abbott RealTime IDH1 is indicated as an aid in identifying acute myeloid leukemia (AML) patients with an isocitrate dehydrogenase-1 (IDH1) mutation for treatment with TIBSOVO® (ivosidenib).

Abbott has submitted a supplement for the expansion of the IU in support of this NDA:

Abbott RealTi*me* IDH1 is indicated as an aid in identifying acute myeloid leukemia (AML) patients with an isocitrate dehydrogenase-1 (IDH1) mutation for treatment with REZLIDHIA (olutasidenib).

The test is for prescription use only.

REZLIDHIA is intended to be used for the treatment of patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase isoform 1 (IDH1) mutation.

III. CDRH RESPONSE TO CDER QUESTIONS

CDRH has reviewed the Abbott Realtime IDH1 Assay for its intended use as a companion diagnostic to identify AML patients with an IDH1 mutation for treatment with REZLIDHIA under P170041/S006 (MDUFA date 6/19/2022). Following review, we have decided that the information provided is acceptable and the sPMA is approvable pending approval of REZLIDHIA.

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215814
Submission Number	001
Submission Date	2/15/2022
Date Consult Received	2/18/2022
Drug Name	Olutasidenib (Rezlidhia capsules)
Indication	IDH1-mutated Acute Myeloid Leukemia
Therapeutic Dose	150 mg BID, fasting
Clinical Division	DHM1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 2/18/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 04/27/2021 under IND 127313 in DARRTS;
- Previous IRT review dated 07/02/2018 under IND 127313 in DARRTS;
- Sponsor's clinical study report # 2102-HEM-101 (SN0001; link);
- Sponsor's cardiac safety report # 2102-HEM-101 (SN0001; link);
- Sponsor's summary of pharmacology (SN0001; link);
- Sponsor's summary of toxicology (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0003; link).

1 SUMMARY

Although no mean increases >20 msec in QTc interval of olutasidenib was detected in this QT assessment at therapeutic exposures, a concentration-dependent increase in QTcF interval was observed. The totality of nonclinical and clinical data indicates a potential for QTc prolongation which is likely mediated through direct interaction with the hERG potassium channel.

The effect of olutasidenib (FT-2102) was evaluated in a sub-study (Study # 2102-HEM-101). This multi-center study evaluated safety, efficacy, pharmacokinetics and pharmacodynamics of olutasidenib as a single agent and in combination with azacytidine or low dose cytarabine. The highest dose evaluated was 150 mg twice daily (as a single agent) under fasting condition, which covers therapeutic exposures (Section 3.1). Data were analyzed using exposure-response analysis as the primary analysis, which indicated a concentration-dependent increase in QTc interval; however, the mean increases was not >20 msec with the proposed therapeutic dose at steady-state (Section 4.5). Since the

exposures observed in this study for 150 mg twice daily were slightly lower than those reported previously at the steady state (Cmax ~3136 ng/mL, under fasting conditions), the predicted effects at estimated Cmax,ss are presented in Table 1.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Cmax, ss (µg/L)	ΔQTcF (msec)	90% CI (msec)
QTc	150 mg Olutasidenib (twice daily, fasting)	3136.0	6.2	(2.7 to 9.7)

For further details of the FDA analysis, please see Section 4.

Considering that olutasidenib exhibits a positive food effect (~2.5-fold), increased QT prolongation is expected with increased exposures of olutasidenib under a fed condition compared to that under fasting condition. The results of non-clinical studies also suggest that olutasidenib has a potential to prolong QT prolongation by direct inhibition of the hERG current at therapeutic exposure (hERG safety margin: 19x). Moreover, QTc prolongation was observed in vivo studies in monkey at exposures of olutasidenib exceeded the high clinical exposures (Section 3.1.2). In addition, the by-time analysis also indicated similar findings (Section 4.3).

In the Phase 1 safety population, there were 4 patients with changes to QTcF to ≥ 500 msec and 7 patients with a change of > 60 msec. Three patients had QTc >500 msec and a change of >60 msec from baseline — all were in the olutasidenib and azacitidine combination therapy cohort.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Considering the totality of nonclinical and clinical information indicating potential for QTc interval prolongation with olutasidenib, we recommend that the Division considers inclusion of relevant information on QTc prolongation in various sections (e.g., food effect, interactions) of the label.

Our review focused on the Phase 1 study and did not evaluate QTc interval or AEs related to QTc prolongation in Phase 2. We defer to the Division on the need to include Warning about QTc prolongation based on AE data from Phase 2.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD SN0001 (link) from the CSS-IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Based on evaluations following a single dose and multiple doses of olutasidenib 150 mg twice daily administered under fasting conditions, the largest mean increase in QTc interval was 6.2 msec (upper confidence interval = 9.7 msec) (b) (4) *33 patients with advanced hematologic malignancies with an IDH1 mutation. The increase in the QTc interval was concentration-dependent.*

QTc interval was not evaluated at high clinical exposures. <TRADENAME> exhibits a positive food effect and increased QT prolongation is expected with increased exposures of olutasidenib under a fed condition compared to that under fasting condition [see Clinical Pharmacology (12.3)].

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Forma Therapeutics, Inc. is developing olutasidenib for the treatment of relapsed or refractory acute myeloid leukemia (with an isocitrate dehydrogenase-1 mutation). Olutasidenib (Rezlidhia, FT-2102; MW: 354.79 g/mol; chiral) is inhibitor of mutated isocitrate dehydrogenase 1 (IDH1).

The product is formulated as immediate-release capsule formulation containing 150 mg olutasidenib for oral administration. The proposed therapeutic dose for the present indication is 150 mg twice daily (every 12 hours, an empty stomach at least (b) (4) before or 2 hours after food; until disease progression or unacceptable toxicity). The peak concentrations of 3136 ng/mL (Tmax: ~2 h; half-life: ~25.2 h) are expected at steady state with the anticipated therapeutic dose (C2D1m Ph2Ch1; Study # 2102-HEM-101). Considerable accumulation is expected at steady state with the proposed maximum therapeutic dose (Cmax Racc: ~5.94). The product exhibits a positive food effect with a 2.5-fold increase in exposure (Cmax: 1285 vs. 441.7 ng/mL for 150 mg single dose) was observed following its administration with a fed compared to that under fasting condition (Study # 2102-HVS-106). The sponsor proposes to administer it under fasting conditions. The studies indicate that olutasidenib is extensively metabolized (primarily by CYP3A4 with lesser contribution from CYP2C8, CYP2C9 and CYP2C19; no major circulating metabolites identified). Metabolic pathways involve N-dealkylation, demethylation, oxidative deamination followed by oxidation, mono-oxidation with subsequent glucuronidation. Concomitant administration of olutasidenib with a strong inhibitor of CYP3A4 (e.g., itraconazole) did not result in significantly increased exposures of olutasidenib (Cmax: 81.58% & AUClast: 94.1%; Study # 2102-HVS-103). The human

mass balance study indicates that 75% of the drug (as TR; 35% unchanged) is excreted in feces, and 17.3% of the drug (as TR; 1% unchanged) is excreted in urine (Study # 2102-HVS-104). Considering that renal excretion is a minor elimination pathway, the sponsor states that renal impairment is not expected to impact olutasidenib exposure and proposes no dose adjustment for patients with mild or moderate renal impairment. However, increased exposure of olutasidenib were observed in subjects with mild (~36%) and moderate (~12%) hepatic impairment compared to those with normal hepatic function (Study # 2102-HVS-105). The sponsor proposes no dose adjustment for patients with mild or moderate hepatic impairment and the proposed label describes that the safety of olutasidenib has not been evaluated in subjects with severe hepatic impairment as well as severe renal impairment.

Previously, the IRT reviewed the sponsor's request for an alternative QT study and planned to exclude mean increases >20 msec with oral administration of olutasidenib (07/02/2018). The sponsor was proposing to use the concentration-QT analysis conducted using ECG/PK data in a subset of patients (n=30) in their ongoing clinical study (Study # 2102-HEM-101). This was a multi-center, open-label, dose-escalation and expansion study evaluating safety, efficacy, pharmacokinetics, and pharmacodynamics of olutasidenib as a single agent and in combination with azacytidine or low dose cytarabine. Patients included in the sub-study were single agent treated patients receiving 150 mg twice daily under fasting conditions. ECG and time-matched PK samples were collected on Cycle 1 Day 1 (pre-dose and 0.5, 1, 2, 4, 8 and 24 h post-dose) and at steady-state Cycle 2 Day 1. The proposed assessment plan was considered reasonable to exclude mean increases >20 msec at the planned therapeutic dose.

3.1.2 Nonclinical Safety Pharmacology Assessments

Olutasidenib had modest activity against the hERG ion channel (IC50 = 11.8 µM) in patch-clamp studies, but was less potent when evaluated against the human Cav1.2 calcium and Nav1.5 sodium channels (IC50 ≥ 43 µM).

The potential for olutasidenib (referred to as FT170 in the report) to induce proarrhythmic activity was further evaluated in the Langendorff perfused rabbit heart model (FT-2102-PH-009). The rabbit heart was chosen as it has been demonstrated that isolated rabbit hearts exhibit similar electrophysiologic responses as the human heart to numerous therapeutic compounds from a variety of classes (Hondeghem, 2001; Hondeghem, 2003). Olutasidenib was screened at up to 30 µM; however, there was no significant dose-dependent shift in QT interval or any other monitored parameter.

The hERG IC50 of 11.8 µM is 17-fold the free maximum observed concentration of 711nM at the efficacious dose of 150 mg BID. Consistent with hERG inhibition noted in vitro, QT interval increases were noted in the 28-day toxicology study in monkeys (see Module 2.6.7, Table 7.1C).

Reviewer's comment: *The sponsor evaluated the effects of FT170 (olutasidenib) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The study report (FT-2012-PH-008; link) describes the potential effects of olutasidenib on the hERG current in HEK293 cells. The hERG current was assessed at room temperature, using an automated QPatch platform. The voltage protocol was not provided in the report. Positive control drug cisapride at 50 nM blocked the hERG current*

by 72.4%. A full blocker (e.g., E-4031 at 1 µM) was not added to the end of the experiment to assess the non-hERG currents evoked by the voltage protocol. Drug concentrations were not verification in the study.

Olutasidenib inhibited the hERG currents by 19.7, 48.9 % 70.6% and 84.5% at 3, 10, 30 and 100 µM, respectively. The IC50 for the inhibitory effect of olutasidenib on hERG current was 11.79 µM.

The sponsor also evaluated the effects of olutasidenib on Cav1.2 and Nav1.5 currents using the same QPatch platform. The IC50s of olutasidenib on Cav1.2 and Nav1.5 were 43.3 µM and > 100 µM, respectively.

The hERG safety margins of olutasidenib on hERG current are summarized below:

Table 2 Safety margin of olutasidenib on hERG Current

	Cmax (ng/mL)	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50 (µM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
Olutasidenib	*3136*	*93%*	*219.5*	*11.79*	*355*	*19x*

Cmax-ss:3136 ng/mL at 150 mg Bid from study 2102-HEM-101.

The in vivo study (2336-008) assessed the potential effects of olutasidenib on ECG parameters when administered via oral gavage for 28 consecutive days and following a 28-day recovery period in monkeys. Olutasidenib -related ECG findings were observed at the highest dose level (300/200/100 mg/kg/day). Doses of 300/200/100 mg/kg/day (300 mg/kg/day: Day 1-Day11. 200 mg mg/kg/day: Day 12 and Day 13. 100 mg/kg/day: Day 14-Day28) were associated with a significant increase in QTc at the Day 1 postdose (7.14% or ~23 ms) and both terminal intervals that became progressively longer with repeat dosing. Compared to pretest values, the magnitude of the increase in the QTc in males at the terminal post-dose interval was 10.61% (~34 ms). The change in the QTc interval was reversible, not being present at the recovery interval. Additionally, ventricular premature complexes and ventricular tachycardia were observed in one animal following the 300/200/100 mg/kg/day dose. The Cmax values were 8500 ng/mL and 10200 ng/mL on Day 1 and Day 28 for 300/200/100 mg/kg/day dose group, respectively. The exposure exceeded (2.7 x to 3.2 x) the clinical exposure (3136 ng/mL). No positive drugs were used in the study.

Another in vivo study (8362180) also evaluated the effects of olutasidenib on ECG parameters when administered twice daily via oral gavage to monkeys. Animals in Groups two through four were administered 30, 70/50, or 150 mg/kg/day, respectively. ECGs were recorded once during the predose phase and once during Week 13 (Day 89) of the dosing phase at approximately 4 hours post the first daily dose. Dosing in group 4 was terminated after 38 days due to adverse clinical observations. The dose level was lowered from 70 to 50 mg/kg/day for Group 3 animals starting on Day 38 of the dosing phase. No olutasidenib -related changes in PR interval, QRS duration, corrected QT (QTc) interval, or heart rate were observed on Day 89 of the dosing phase in animals administered 30 or 50 mg/kg/dose.

The Cmax values were 3210 ng/mL and 5240 ng/mL on Day 88, at doses 30 and 50 mg/kg/day, respectively. The exposure exceeded (1.0x to 1.7x) the clinical exposure (3136 ng/mL). No positive drugs were used in the study.

In summary, the hERG assay showed deviations (e.g., room temperature, lack of drug concentration verification, and lack of a full blocker at the end of the experiments) from the best practice recommendations for an in vitro assay according to the new ICH S7B Q&As 2.1. The results show that olutasidenib has a potential to prolong QT prolongation by direct inhibition of the hERG current at therapeutic exposure (hERG safety margin: 19x). The limitations of the assay may impact the hERG safety margin (e.g., decrease the IC50 value and lower the hERG safety margin). QTc prolongations were observed at exposures exceeded the high clinical exposure in monkeys. Additionally, ventricular tachycardias were observed in one animal following the 300/200/100 mg/kg/day dose. The QTc prolongations observed in the in vivo monkey study are likely mediated by direct interaction with the hERG current.

3.2 SPONSOR'S RESULTS

The results are shown for the ECG substudy (n=33) in Study 2102-HEM-101 Phase 1.

3.2.1 By-Time Analysis

The primary analysis for olutasidenib was based on exposure-response analysis, please see Section 3.2.3 for additional details.

Sponsor's report shows the LS mean ΔQTcF on cycle 1 day 1 ranged from -1.7 to 4.7 ms. The LS mean ΔQTcF on cycle 2 day 1 ranged from 4.0 to 10.8 ms.

Reviewer's comment: *The trend shown in the by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

Sponsor only reports outlier analysis results for 150 mg olutasidenib dose group. There was one subject experienced QTcF greater than 500 ms. There were two subjects experienced PR greater than 200 msec with an increase in ΔPR >25%, three subjects experienced HR greater than 100 bpm with an increase in ΔHR >25%, and one subject experienced QRS greater than 100 ms with an increase in ΔQRS >25%.

Reviewer's comment: *FDA reviewer's analysis results are similar to sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

As a primary analysis, the sponsor performed PK/PD analysis to exploring the relationship between concentration of olutasidenib and ΔQTcF (change from baseline in QTcF) in a sub-study using a linear mixed-effects approach.

The sponsor analysis indicates a concentration dependent increase in QTcF with a slight positive slope of 0.0017 msec/ng/mL (90% CI 0.00044 to 0.00294 msec/ng/mL; *statistically significant*). The model predicted ΔQTcF (upper confidence interval) values of 6.10 (9.34) msec at the mean peak concentrations for the highest dose studied (150 mg twice daily; C2D1: geomean Cmax ~3066 ng/mL; C2D1) following twice daily administration as monotherapy. The results of the sponsor's analysis did not suggest that olutasidenib is associated with mean increases >20 msec in the QTcF interval at the proposed therapeutic dose (i.e., 150 mg twice daily).

Reviewer's comment: *Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis Related to QT Prolongation

In Study 2102-HEM-101 Phase 1, the safety population consists of 78 patients included in the Phase 1 SAS, highlighting the RP2D of 150 mg BID olutasidenib. The safety data are presented with a cutoff date of 18 Jun 2020.

TEAEs related to the 'Cardiac Disorder' SOC occurred in 30 (38%) patients. Those cardiac TEAEs that could be related to QTc prolongation included 2 patients had non-serious arrhythmias (no details provided), 2 patients had serious cardiac arrests (1 fatal) and 5 patients had nonserious palpitations. Both cardiac arrests and arrhythmias were not considered treatment-related.

The AESI of QT prolongation was defined by the MedDRA PT of ECG QT prolonged. An ECG QT prolonged TEAE was reported in 3 (4%) patients overall; all were in the olutasidenib and azacitidine combination therapy cohort. Two patients reported Grade 3 events, and the TEAE was assessed as treatment-related in one of these patients. There were no Grade 4 or Grade 5 events of QT prolongation. No events led to dose reduction or discontinuation.

In the Phase 1 patients, ECGs were obtained on Day 1 of Cycles 1 and 2 at pre-dose and at 2, 4 and 8 hours after dosing; ECGs were also obtained on Days 8, 15 and 22 of Cycles 1 and 2 and then at the start of every cycle thereafter. There were 4 patients with changes to QTcF to ≥ 500 msec and 7 patients with a change of > 60 msec. Three patients had QTc >500 msec and a change of >60 msec from baseline.

- Patient (b) (6) (olutasidenib 150 mg BID in combination with azacitidine), a 70-year-old female patient with R/R MDS, had a mean QTcF interval at baseline (pre-dose C1D1) of 397 msec. Average QTc intervals of > 60 msec change from baseline were noted for all ECG measurements from Study Day 400 onward. No TEAEs of ECG QT prolonged were reported. The patient was ongoing as of data cutoff.
- Patient (b) (6) (olutasidenib 150 mg BID in combination with azacitidine), a 68-year-old female patient with treatment-naïve MDS, had a mean QTcF interval at baseline

(pre-dose C1D1) of 380 msec. Sinus tachycardia, minimal voltage criteria for LVH, and borderline ECG abnormalities were noted. On Study Days 22 and 40, average QTc intervals were 444 msec (an increase of 64 msec) and 546 (an increase of 166 msec), respectively; these were both notable as a >60 msec change from baseline, while the Day 40 reading was additionally notable as a shift in value to > 500 msec from a baseline QTcF of ≤ 480 msec. Electrocardiograms on Study Day 22 were noted as normal, while abnormal findings noted on Study Day 40 were LVH with repolarization abnormality and prolonged QT. A Grade 3 TEAE of ECG QT prolonged was reported and assessed as unrelated to either olutasidenib or azacitidine; it was treated with an oral magnesium supplement and resolved on Study Day 48. The patient last took azacitidine on Study Day 133 and olutasidenib on Study Day 160, and discontinued treatment for HSCT transplantation. The patient died on Study Day 223 due to complications from the transplant.

- Patient (b) (6) (olutasidenib 150 mg BID in combination with azacitidine), a 66-year-old male patient with R/R AML, had a mean QTcF interval at baseline (pre-dose C1D1) of 423 msec. Abnormalities of LVH with repolarization abnormality and inferior infarct, and age undetermined were noted. On Study Day 23, the average QTcF of 536 msec (an increase of 113 msec) was notable as both a > 60 msec change from baseline and a shift in value to > 500 msec from a baseline QTcF of ≤ 480 msec; in addition to the abnormalities noted at baseline, prolonged QT was noted on this day. A TEAE of ECG QT prolonged was not reported. On Study Day 29 (C2D1 pre-dose), the average QTcF had decreased to 412 msec and did not demonstrate a > 60 msec change from baseline or a shift in value to > 500 msec again during subsequent visits. The patient last took azacitidine on Study Day 35 and olutasidenib on Study Day 56, and discontinued treatment due to progressive disease. The patient died on Study Day 68.

Reviewer's comment: *QTc prolongation occurred in patients taking combination of* olutasidenib and azacytidine). *Azacitidine for SC or IV injection has been approved since 2004, but does not contain a description of its effect on the QTc interval.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

Thirty-three subjects treated by 150 mg olutasidenib with Holter ECG data were included in by-time analysis, exposure-response analysis, and categorical analysis.

4.2.1 Quality

Digital ECG acquisition and interpretation appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different cycles. The maximum ΔQTcF values by cycle are shown in Table 3.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

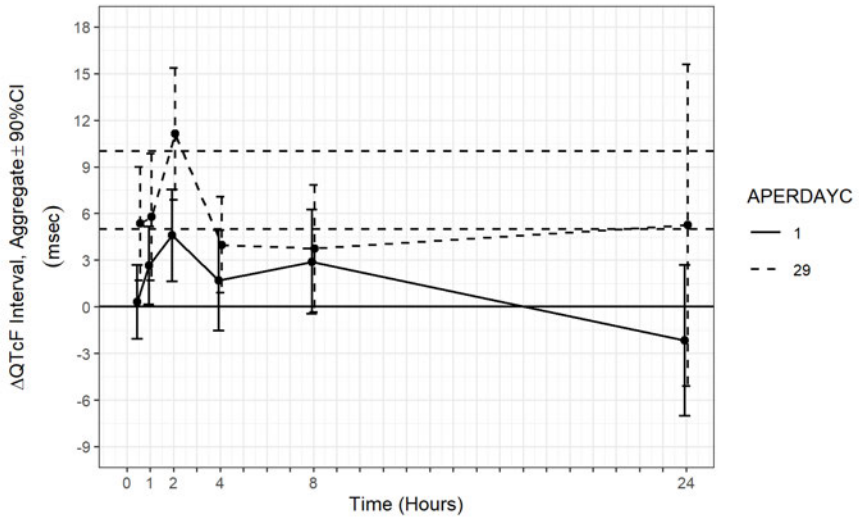


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTcF (msec)	90.0% CI (msec)
150 mg olutasiden b	1	33	2.0	4.6	(1.6 to 7.5)
150 mg olutasiden b	29	32	2.0	11.1	(6.9 to 15.4)
150 mg olutasiden b	29	11	24.0	5.2	(-5.1 to 15.6)

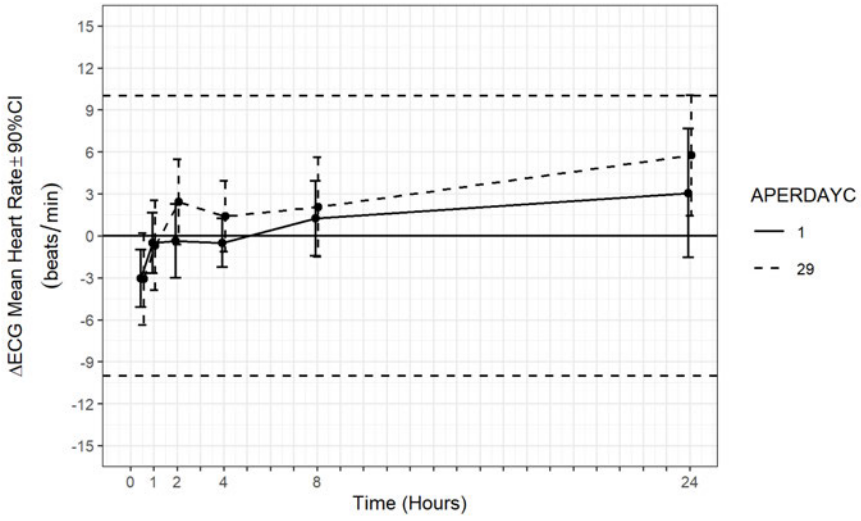
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different cycles.

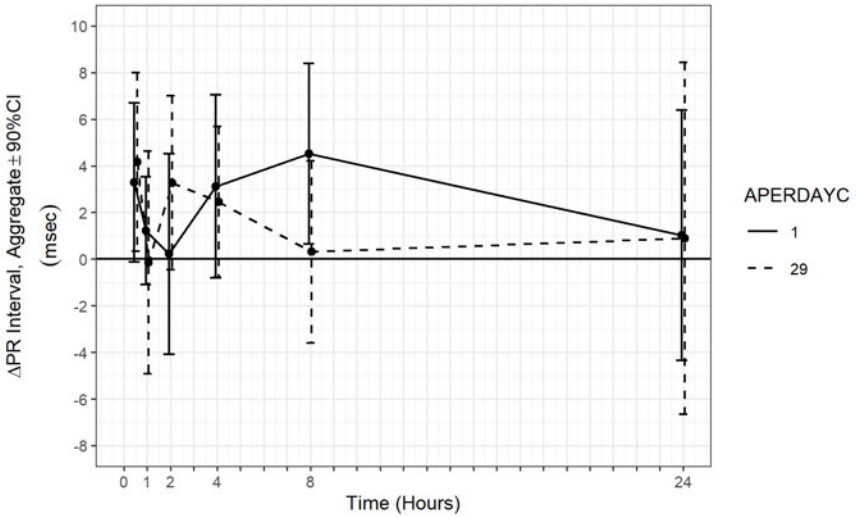
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different cycles.

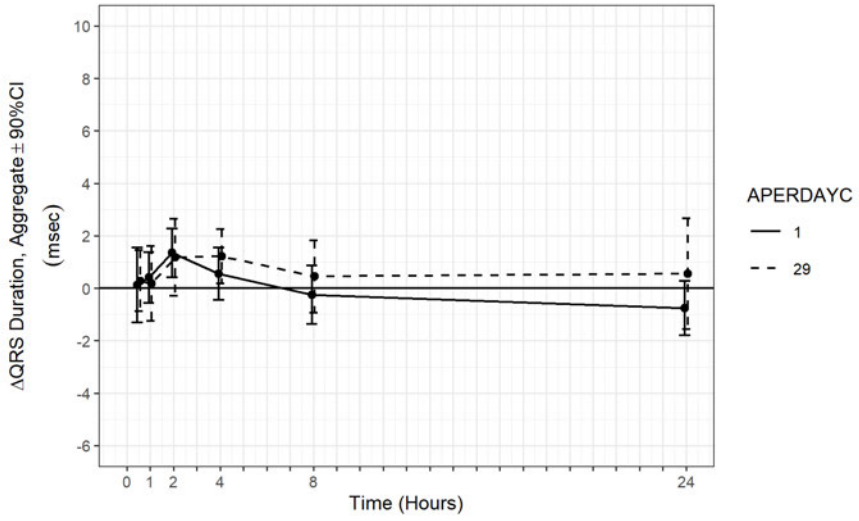
Figure 3: Mean and 90% CI of ΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different cycles.

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In this phase 1/2 study, patients will be given FT-2101 daily in continuous 28-day cycles, alone or in combination with azacytidine or LDAC until treatment discontinuation. The one subject with treatment combination of FT-2101 and azacytidine is not included in this study. Categorical analysis results are reported only for treatment without combination of azacytidine. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 4 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec with or without a change from baseline >60 msec. There was one subject in 150 mg olutasidenib dose group experienced QTcF greater than 500 msec. There were no subjects with ΔQTcF >60 msec.

Table 4: Categorical Analysis for QTcF (maximum)

Actual Treatment	Total (N)		Value <=450 msec		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & <=60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
150 mg olutasidenib	33	450	25 (75.8%)	391 (86.9%)	6 (18.2%)	53 (11.8%)	1 (3.0%)	5 (1.1%)	1 (3.0%)	1 (0.2%)

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). Five subjects experienced HR greater than 100 beats/min in 150 mg olutasidenib dose group. Four of these subjects also had HR increases from baseline >25%.

Table 5: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
150 mg FT-2101	33	450	28 (84.8%)	436 (96.9%)	5 (15.2%)	14 (3.1%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (≤220 msec, and >220 msec with or without 25% increase over baseline). Two subjects in 150 mg olutasidenib dose group experienced PR greater than 220 msec and 25% increase over baseline.

Table 6: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
150 mg FT-2101	33	450	29 (87.9%)	434 (96.4%)	2 (6.1%)	13 (2.9%)	2 (6.1%)	3 (0.7%)

4.4.4 QRS

There were no subjects with QRS >120 msec and 25% increase over baseline.

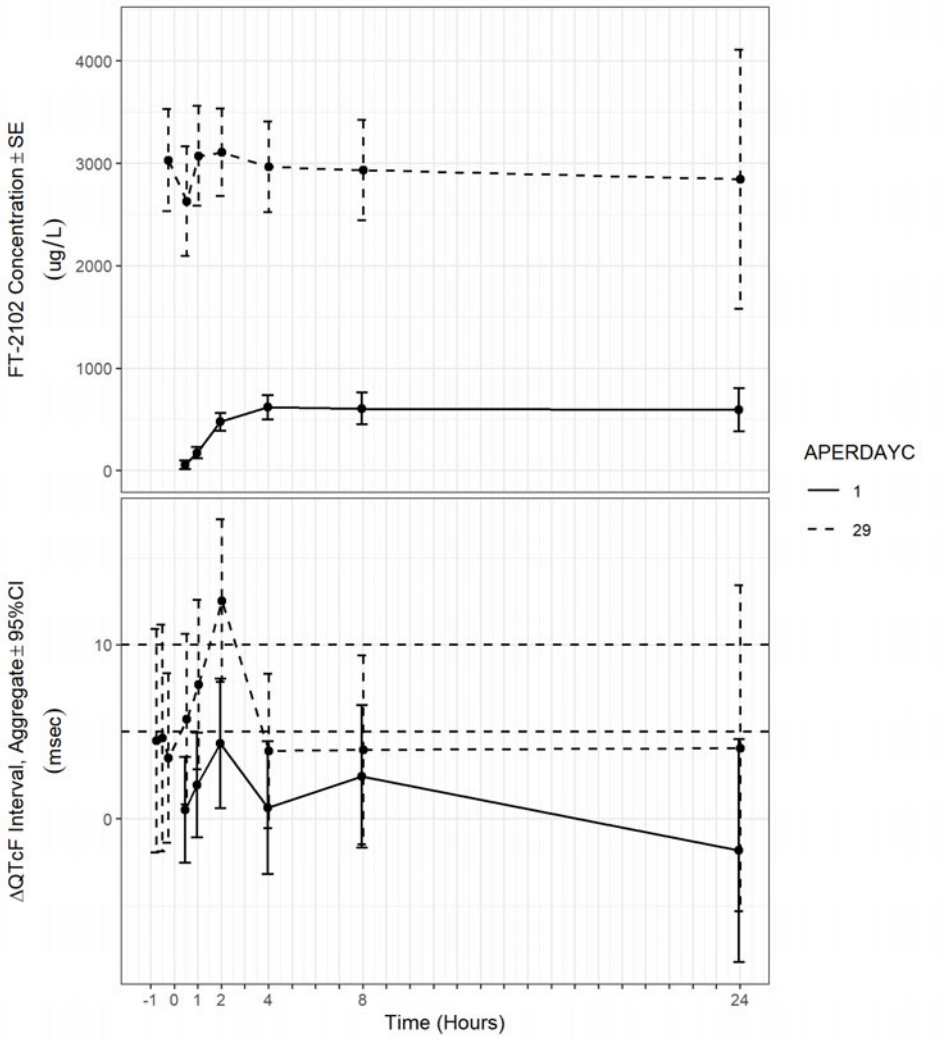
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of this analysis was to assess the relationship between plasma concentration of olutasidenib and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between olutasidenib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between olutasidenib concentration and ΔQTcF and 3) a non-linear relationship.

An evaluation of the time-course of olutasidenib concentration and changes in ΔQTcF is shown in Figure 5.

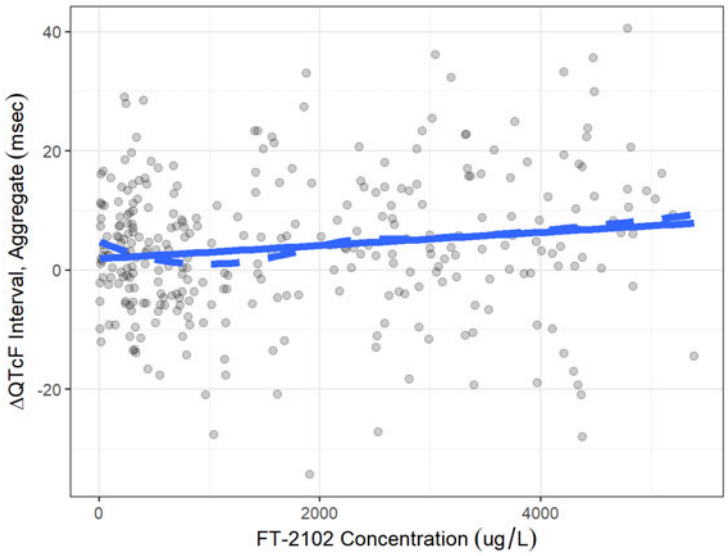
Figure 5: Time-course of Olutasidenib Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

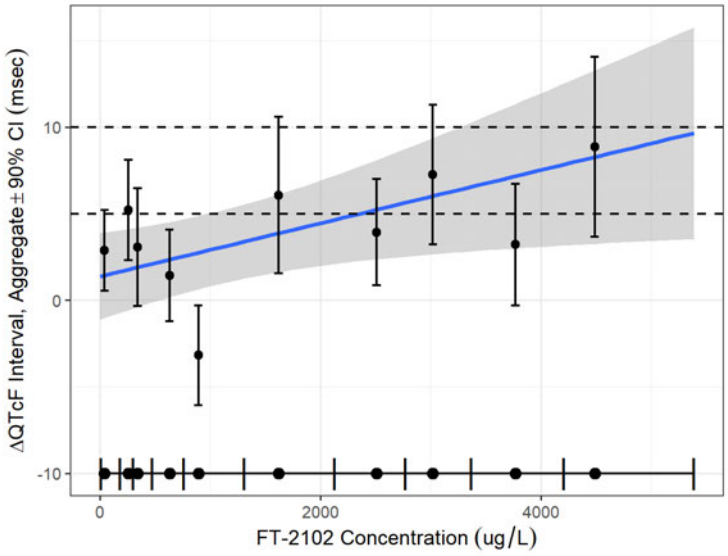
There was no apparent delay between the time at maximum effect on ΔQTcF and peak concentrations of olutasidenib indicating no significant hysteresis. Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes and the maximum change in heart rate is below 10 bpm (Section 4.3.2).

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between olutasidenib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between olutasidenib concentration and ΔQTcF and supports the use of a linear model.

Figure 7: Goodness-of-fit Plot for QTcF



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 7. The exposures observed in this study were slightly lower than those reported previously. The

model predicted ΔQTcF (and confidence intervals) at the peak concentrations for the proposed therapeutic dose (i.e., 150 mg twice daily; Cmax ~3136 ng/mL, under fasting conditions) at the steady state are described in Table 1.

Table 7: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Olutasidenib Concentration (ug/L)	ΔQTcF (msec)	90.0% CI (msec)
150 mg olutasidenib	1	655.5	2.4	(0.2 to 4.5)
150 mg olutasidenib	29	3018.8	6.0	(2.7 to 9.4)

4.6 SAFETY ASSESSMENTS

See Section 3.2.4. No additional safety analyses were conducted.

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/s/

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